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VOL. 22, SEC. B. JULY, 1944 NUMBER 4

THE SYNTHESIS OF POSSIBLE DEGRADATION PRODUCTS OF METATHEBAINONE. II.[1]

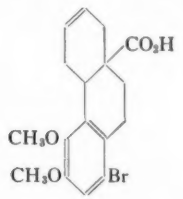
BY H. L. HOLMES[2] AND L. W. TREVOY[3]

Abstract

The poor yield of β-(3,4-dimethoxybenzoyl)-propionic acid obtained from the condensation of equimolar quantities of veratrole and succinic anhydride by two moles of aluminium chloride is due to the demethylation of the C_4-methoxyl group. The phenolic acid has been isolated and its structure established by degradation to 3-methoxy-4-ethoxybenzoic acid. The yield of the dimethoxy-acid has been improved to 83% by modifying the usual procedure for this reaction.

Introduction

In extending the work outlined in the writers' previous paper (9) to the synthesis of 1-bromo-3,4-dimethoxy-5,8,9,10,13,14-hexahydrophenanthrene-14-carboxylic acid (I), a considerable quantity of β-(3,4-dimethoxybenzoyl)-propionic acid (II) (R=R′=OCH_3) was required as starting material. This



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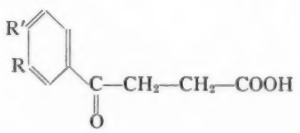

(II)

keto-acid has been prepared by Bargellini and Giua (2), Dalal and Nargund (3), Fieser and Hershberg (4) and Haworth and Mavin (7) under a variety of conditions and in yields varying from 40 to 73%. Fieser and Hershberg reported that in the preparation of β-(alkoxybenzoyl)-propionic acids the best results were obtained when equimolar quantities of succinic anhydride and the alkoxybenzene in nitrobenzene–tetrachloroethane solution were condensed using two moles of aluminium chloride. Even under the most favourable conditions the yield of β-(3,4-dimethoxybenzoyl)-propionic acid was

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Contribution from the Department of Chemistry, University of Saskatchewan, Saskatoon, Sask., based on a thesis submitted by L. W. Trevoy to the Committee on Graduate Studies, in partial fulfilment of the requirements for the degree of Master of Arts, April, 1943.

[2] *Assistant Professor of Chemistry, University of Saskatchewan.*

[3] *Graduate student at the University of Saskatchewan and holder of a Bursary under the National Research Council of Canada, 1941–1942, and a Studentship, 1942–1943.*

only 67%, and if the reaction was carried out at room temperature the yield fell to 54% of the theoretical amount. These workers also observed that the yield was less favourable (40%) when three moles of condensing agent was employed. This may be accounted for by the observation of Adams and Gross (1) that increased amounts of aluminium chloride tended to give more demethylation during the condensation of propionic anhydride with 3,5-dimethylanisole. These results are in marked contrast with the 85% recovery of β-(4-methoxybenzoyl)-propionic acid obtained under comparable conditions from anisole and succinic anhydride.

In an effort to account for the remainder of the reagents in the above reaction, the aqueous mother liquors from the steam distillation of the solvent, after removal of the β-(3,4-dimethoxybenzoyl)-propionic acid, was concentrated and an additional amount of a solid acid, differing from the desired keto-acid, was recovered in about 23% yield. The greater solubility of the secondary acid product in water indicated that it was a phenolic acid and that demethylation had occurred. This proved to be the case, for the ethyl ester, but not the acid itself, gave a bright green coloration with ferric chloride solution. The preparation of this secondary product* from guaiacol and succinic anhydride and its conversion to β-(3,4-dimethoxybenzoyl)-propionic acid is sufficient to establish that it is a β-(hydroxymethoxybenzoyl)-propionic acid with substituents at the C_3 and C_4 positions of the benzene ring. Neither β-(3-hydroxy-4-methoxybenzoyl)-propionic acid (II) (R = OH, R′ = OCH_3) nor the β-(3-methoxy-4-hydroxybenzoyl)-propionic acid (II) (R = OCH_3, R′ = OH) appears to have been prepared, but Haworth and Kelly (6) have prepared β-(3-methoxy-4-ethoxybenzoyl)-propionic acid (II) (R = OCH_3 and R′ = OC_2H_5), from ethyl 3-methoxy-4-ethoxybenzoylacetate and ethyl bromoacetate and report a melting point of 136 to 137° C. for this acid. No analytical figures, other than the neutralization equivalent, were given. For comparison the ethyl ether of the phenolic acid, $C_{13}H_{16}O_5$, m.p. 139 to 140° C., was prepared. This ethylated acid is probably identical with the ethoxy acid of Haworth and Kelly. To remove the possibility that it was the isomeric 3-ethoxy-4-methoxybenzoyl-propionic acid (II) (R = OC_2H_5, R′ = OCH_3), the acid was oxidized with an alkaline permanganate solution to the corresponding benzoic acid, which melted at 192 to 193°. This must be 3-methoxy-4-ethoxybenzoic acid (m.p. 193 to 194° C. (5)), since 3-ethoxy-4-methoxybenzoic acid melts at 165° C. (11). The 3-methoxy-4-ethoxybenzoic acid and its amide were prepared from vanillin (5, 10), and no depression of the melting points was observed on admixture of the two samples of the acid and the amide.

Much of the demethylation in this reaction occurs during the steam distillation, for if the hydrochloric acid solution of aluminium chloride is separated from the nitrobenzene and tetrachloroethane prior to the steam distillation the yield of β-(3,4-dimethoxybenzoyl)-propionic acid is improved by 16%.

** This acid has been prepared by Mr. J. G. Jeffrey in poor yield from guaiacol and succinic anhydride under conditions used for the synthesis of β-(3,4-dimethoxybenzoyl)-propionic acid.*

Methylation of β-(3-methoxy-4-hydroxybenzoyl)-propionic acid gives an over-all yield of 84.8% of the fully methylated γ-keto acid.

The reduction of the γ-keto acids to the corresponding butyric acids (12) and their conversion to the ethyl esters presents no difficulties.

Experimental*

β-(3,4-Dimethoxybenzoyl)-propionic Acid

The procedure used for the preparation of β-(3,4-dimethoxybenzoyl)-propionic acid from 103.5 gm. of veratrole (b.p. 202 to 204.5° C.) (720 mm.) and 78.8 gm. of succinic anhydride was that described by Fieser and Hershberg (4). After removing the nitrobenzene and tetrachloroethane by steam distillation, 127.0 gm. of the acid crystallized from the hot water. The aqueous filtrate from the first crystallization, when concentrated to about one litre, yielded a second crop of coloured, solid material weighing 25.0 gm.

A portion of the second crop (β-(3-methoxy-4-hydroxybenzoyl)-propionic acid) was methylated with dimethyl sulphate. After methylating an alkaline solution of 11.2 gm. of the acid at 80° C. with 6.5 cc. of dimethyl sulphate, the aqueous solution was decolorized with Norit, cooled, and acidified. The pale cream-coloured β-(3,4-dimethoxybenzoyl)-propionic acid that precipitated melted at 142 to 144° C. After one crystallization from water 11.0 gm. (92.4%) of the acid was recovered; m.p. 152.5 to 155.5° C. This improved the over-all yield of the dimethoxy-acid from 67% (4) to 84.8% and the acid was sufficiently pure for reduction to γ-(3,4-dimethoxyphenyl)-butyric acid.

In more recent work the demethylation has been virtually eliminated by steam distilling only the nitrobenzene-tetrachloroethane solution after decomposition of the aluminium chloride complex. In this way 82.7% of β-(3,4-dimethoxybenzoyl)-propionic acid may be recovered directly from the condensation of succinic anhydride with veratrole.

β-(3-Methoxy-4-hydroxybenzoyl)-propionic Acid

The dark crystalline second crop of solid (9.0 gm.) from the preparation of β-(3,4-dimethoxybenzoyl)-propionic acid was esterified by the Fischer-Speier method. The ester was distilled and the fraction boiling at 140 to 144° C. (19 mm.) (7.0 gm., 70%) was collected. The viscous oily ester gave a green coloration with aqueous alcoholic ferric chloride, indicating the presence of a phenolic group in the ester.

Two grams of the ethyl ester was saponified with 10% sodium hydroxide solution and upon acidification of the alkaline solution 1.04 gm. of the hydroxy-acid was recovered. The acid was twice recrystallized from water, forming clusters of fine white needles that melted at 131.0 to 131.5° C. Contrasted with the ester, the hydroxy-acid failed to give a coloration with ferric chloride

* *All melting points were taken in an apparatus designed by E. B. Hershberg (8) and are corrected unless otherwise stated.*

solution. Calc. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.36%. Found: C, 58.80; H, 5.23%.

γ-(3-Methoxy-4-hydroxyphenyl)-butyric Acid

Ten grams of β-(3-methoxy-4-hydroxybenzoyl)-propionic acid was reduced to the corresponding butyric acid with amalgamated zinc and hydrochloric acid (12). The reduction product (5.0 gm.) was twice recrystallized from chloroform and petroleum ether and melted at 108 to 109° C. To obtain an analytical sample, the acid was converted to the ethyl ester and the fraction boiling at 209 to 211° C. (23 mm.) was collected. Saponification of the ester gave an oil, which, after extraction with ether, was crystallized from chloroform and petroleum ether. The feathery plates of γ-(3-methoxy-4-hydroxyphenyl)-butyric acid melted at 114 to 116° C. Calc. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.68; H, 6.88.

The ethyl ester gave a deep green coloration with aqueous alcoholic ferric chloride solution.

β-(3-Methoxy-4-ethoxybenzoyl)-propionic Acid

The β-(3-methoxy-4-hydroxybenzoyl)-propionic acid (0.180 gm.) was ethylated in a solution of 0.15 gm. of potassium hydroxide in 3 cc. of water, with an excess of diethyl sulphate. The diethyl sulphate was added dropwise to the alkaline solution, which was heated to 80° C., and the mixture shaken from time to time. The cold alkaline solution, after extracting with ether, was acidified with hydrochloric acid, and 0.175 gm. (86.4%) of β-(3-methoxy-4-ethoxybenzoyl)-propionic acid was collected, washed, and dried; m.p. 136 to 138° C. The ethylated acid crystallized from water in slender colourless needles 2 cm. long and melted at 139 to 140° C. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39; neut. equiv., 252.2. Found: C, 61.50; H, 6.24; neut. equiv. 251.3.

For this acid Haworth and Kelly (6) report a melting point of 136 to 137° C. and a neutralization equivalent of 248.

3-Methoxy-4-ethoxybenzoic Acid

A. Five grams of ethyl β-(3-methoxy-4-hydroxybenzoyl)-propionate was dissolved in warm (60 to 70° C.) 10% sodium hydroxide solution and ethylated with diethyl sulphate. Without further purification the oily product was oxidized with alkaline potassium permanganate solution and the excess oxidizing agent reduced with sodium bisulphite to manganese dioxide, which was removed by filtration. Upon acidification of the filtrate a yellow solid precipitated which when collected, washed, and dried, weighed 0.92 gm. After several crystallizations from 300 cc. of water, a constant melting point of 192 to 193° C. (uncorr.), 194.9 to 195.9° C. (corr.) was reached. Calc. for $C_{10}H_{12}O_4$: neut. equiv., 196.2. Found: neut. equiv., 197.4.

The amide, which was prepared from this acid, crystallized from water in long needles and melted at 181.5 to 182.5° C.

B. This acid was also prepared by a four-step synthesis from vanillin. The 3-methoxy-4-ethoxybenzonitrile was prepared, following the general method of Johnson and Stevenson (10) for the synthesis of veratronitrile, and the nitrile hydrolysed to 3-methoxy-4-ethoxybenzoic acid by the method of Hann (5).

Diethyl sulphate (9.36 gm.) and a solution of 4.0 gm. of sodium hydroxide in 6.5 cc. of water were added simultaneously and at the same rate to 6.5 gm. of stirred molten vanillin. The reaction mixture was warmed on the steam cone for 15 min. and then allowed to stand in the icebox overnight. It was then collected on a small Hirsch funnel. The ethylated product crystallized from aqueous ethanol in dense prisms and melted at 63.5 to 64.5° C. The yield was 3.66 gm. (47.5%).

The oxime of 3-methoxy-4-ethoxybenzaldehyde was prepared by dissolving 3.66 gm. of the ethylated aldehyde in 8.1 cc. of ethanol and adding this to 3.6 cc. of a water solution of 1.2 gm. of hydroxylamine hydrochloride and 1.2 gm. of sodium hydroxide. When the reaction mixture had stood at room temperature for 2.5 hr., 10 gm. of ice was added and the oxime precipitated by saturating the solution with carbon dioxide. The 3-methoxy-4-ethoxybenzaldoxime, weighing 3.3 gm. (83.2%), was crystallized from water in fine colourless needles. The pure oxime melted at 99 to 100° C.

The 3-methoxy-4-ethoxybenzonitrile was prepared by dehydrating 3.2 gm. of the oxime in 4.0 gm. of acetic anhydride. After the initial reaction had subsided the solution was refluxed gently for 20 min. before it was poured into 13 cc. of cold water. The nitrile, 3.0 gm. (95%), after several crystallizations from water, melted at 102.5 to 103.5° C.

Hydrolysis to the acid occurred when 2.0 gm. of 3-methoxy-4-ethoxybenzonitrile was boiled for several hours with 20% sodium hydroxide solution. The alkaline solution was poured on to ice and after the removal of any unchanged nitrile in ether, it was acidified with hydrochloric acid. The acid, when collected and dried, weighed 1.9 gm. (85.9%). Two recrystallizations from benzene raised the melting point to 192 to 193° C. (uncorr.). A mixture of this acid with that from the oxidation of β-(3-methoxy-4-ethoxybenzoyl)-propionic acid melted at 192 to 193° C. (uncorr.).

The amide, prepared from the above acid, crystallized from water in rosettes of small needles and melted at 182 to 183° C. A mixture of this amide and that prepared from the oxidation reaction melted at 182.0 to 182.5° C.

The percentage yield of the intermediate products in this synthesis is recorded in Table I, and the melting points of the intermediates are listed along with those reported by Hann (5).

γ-(3,4-Dimethoxyphenyl)-butyric Acid

The ketone group of β-(3,4-dimethoxybenzoyl)-propionic acid was reduced by the Clemmensen method (12). From 16.3 gm. of the γ-keto acid 12.2 gm. (79.5%) of the crystalline reduced acid was recovered from the toluene solution which melted at 54.3 to 57.0° C. An additional 1.5 gm. (10%

of somewhat impure acid was recovered from the aqueous liquors of the reaction.

TABLE I

YIELDS AND MELTING POINTS OF THE INTERMEDIATE PRODUCTS IN THE SYNTHESIS OF 3-METHOXY-4-ETHOXYBENZOIC ACID

	Yield, %	Melting points, °C. (uncorr.)	Melting points, °C. (uncorr.) Reported by Hann
3-Methoxy-4-ethoxybenzaldehyde	47.5	63.5 – 64.5	64 – 65
3-Methoxy-4-ethoxybenzaldoxime	82.3	99 – 100	102* 98†
3-Methoxy-4-ethoxybenzonitrile	95	102.5 – 103.5	102
3-Methoxy-4-ethoxybenzoic acid	85.9	192 – 193	193 – 194

* *Anti-3-methoxy-4-ethoxybenzaldoxime.*
† *Syn-3-methoxy-4-ethoxybenzaldoxime.*

By esterifying 25.0 gm. of γ-(3,4-dimethoxyphenyl)-butyric acid by the Fischer–Speier method, 22.0 gm. (79.2%) of the ethyl ester, boiling at 203 to 207° C. (20 mm.), was collected.

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SOME DERIVATIVES OF DIALKOXY-PHTHALIDES[1]

By Richard H. F. Manske[2] and Archie E. Ledingham[3]

Abstract

Treatment of certain dialkoxy-benzoic acids was found to yield dialkoxy-phthalides containing a chloromethyl group. The constitutions of a number of these compounds have been elucidated by unambiguous syntheses. *Inter alia*, it was observed that the Fries rearrangement of 4-acetoxy-3-methoxy-toluene yielded exclusively a *m*-hydroxy-acetophenone. This appears to be the only recorded case of an exclusive meta-rearrangement. Several intermediate aldehydes and some compounds derived from them are described.

Introduction

In a communication dealing with hunnemanine (4) a simple synthesis of 2-methyl-3-ethoxy-4-methoxy-benzaldehyde was described. Before the recorded synthesis was achieved a number of alternate routes to the corresponding acid had been explored, with the result that some hitherto unknown compounds were obtained. The constitutions of a number of them were in doubt and in order to elucidate them it was necessary to prepare some of them by unambiguous methods. As the result of this work many compounds hitherto accessible only with difficulty are now readily available.

When 2 : 3-dimethoxy-benzoic acid (I) is heated with formaldehyde and hydrochloric acid the expected 3 : 4-dimethoxy-phthalide is not obtained in more than traces, the main reaction product being a chloromethyl derivative of the latter. The corresponding 2-ethoxy-3-methoxy acid (II) behaved similarly but it was not possible to find experimental conditions that would yield the desired phthalide, even in small amounts. The chloromethyl compounds could be readily reduced to the methyl compounds and each of these could have two possible formulae. Those having the methyl groups meta to the carboxyl ((V) and (X) respectively) were preferred and were ultimately synthesized. Before this was accomplished attempts were made to prepare 2 : 3-dimethoxy-5-methyl-phthalide by condensing 3 : 4-dimethoxy-6-methyl-benzoic (VI) acid with formaldehyde which on oxidation should yield 3 : 4-dimethoxy-6-methyl-phthalic acid, identical with the oxidation product of (V). Here again the reaction failed to give the simple phthalide. The product was a complex mixture containing halogen, but no single substance could be isolated in reasonable yield.

When 2 : 3-dimethoxy-5-methyl-benzoic acid (VIII), however, was condensed with formaldehyde it gave the phthalide (V) in virtually quantitative

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[2] *Formerly Chemist, National Research Laboratories; now Director of the Research Laboratory, Dominion Rubber Co., Ltd.*

[3] *Formerly Laboratory Assistant, National Research Laboratories; now Chemist, Research Laboratory, Dominion Rubber Co., Ltd.*

yield, no chloromethyl derivative being formed in detectable quantities. The corresponding 2-ethoxy-acid (IX) similarly yielded the phthalide (X), and these two compounds were identical respectively with those obtained via the chloromethyl compounds (III) and (IV) from the acids (I) and (II).

Although 2 : 3-dimethoxy-5-methyl-benzoic acid (VIII) is already known, its preparation in quantity by the published procedure (2) is tedious and the yields are poor. The first attempt to obtain it yielded an isomer. The acetyl derivative (XII) of creosol (XI) when subjected to the Fries rearrangement gave a good yield (70% of purified product) of a hydroxy-acetophenone that did not give a colour with ferric chloride. Moreover it could be methylated with extraordinary facility and therefore did not appear to be an *o*-hydroxy-acetophenone. The methylated ketone could not be directly oxidized to the corresponding acid but this was achieved by first converting it into its isonitroso-derivative and decomposing the latter with alkali. The acid thus obtained was identical with 3 : 4-dimethoxy-6-methyl-benzoic acid (VI) and therefore the product of the Fries rearrangement is 3-hydroxy-4-methoxy-6-methyl-acetophenone (XIII). As far as the authors are aware this is the first known case in which the Fries reaction has yielded the meta compound exclusively. Even the small amount of dihydroxy-ketone formed as the result of demethylation was shown to be the 3 : 4-dihydroxy-ketone.

Attempts to convert creosol into 2-hydroxy-3-methoxy-5-methyl-benzaldehyde by various modifications of the Gattermann reaction yielded no aldehyde whatever, but the recent *o*-hydroxy-aldehyde synthesis of Duff (1) gave the desired compound (XV) in satisfactory yield. It was methylated and the dimethoxy-aldehyde (XVI) oxidized to the corresponding acid (VIII). The ethylation proceeded with greater difficulty but the aldehyde (XVII) and the corresponding acid (IX) were nevertheless obtained by this route.

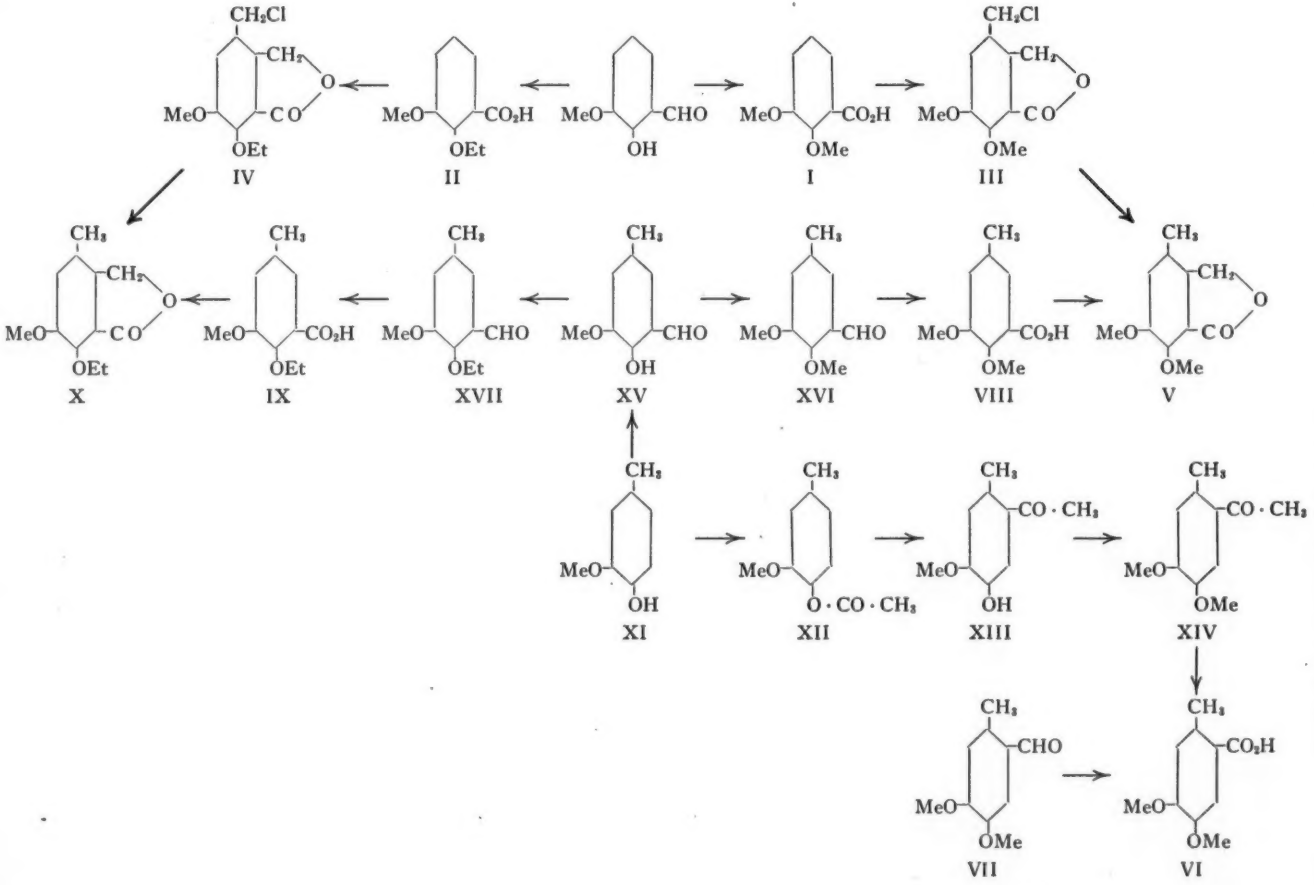
Attempts have been made to make this series of compounds as complete as possible. The new aldehydes have been characterized as their oximes and condensed with malonic acid to yield the corresponding cinnamic acids. The latter were reduced to their dihydro-derivatives. A number of by-products and some additional derivatives are described in the experimental section.

Experimental

3 : 4-Dimethoxy-6-chloromethyl-phthalide (III)

A mixture of 2 : 3-dimethoxy-benzoic acid (I) (25 gm.), hydrochloric acid (40 cc.), and 40% formaldehyde (25 cc.) was boiled under reflux for 30 min. and the cooled mixture extracted with ether. The extract was washed with water, then with aqueous sodium bicarbonate, and again with water. The residue from the ether extract crystallized largely on cooling but it proved to consist of a mixture. Fractional crystallization first from acetone and then from ether yielded colourless plates melting at 106° C.* (yield, 8 gm.).

* *All melting points are corrected.*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CH2
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XVI
VIII
V
CH3
CO · CH3
O · CO · CH3
XI
XII
XIII
XIV
VII
VI

Calc. for $C_{11}H_{11}O_4Cl$: C, 54.43; H, 4.54%. Found: C, 54.24, 54.43; H, 4.40, 4.60%.

The combined filtrates from the crystallization of the above compound were diluted with water and boiled to expel organic solvents. A sparingly soluble crystalline deposit separated from the hot solution. This was recrystallized from hot acetic acid, and it then melted at 213° C. It is sparingly soluble in ether, acetone, and ethanol, and analysis indicates that it is di(3-carboxy-2-hydroxymethyl-4 : 5-dimethoxybenzyl)-ether dilactone. Found: C, 61.38, 61.46; H, 5.30, 4.97%. Calc. for $C_{22}H_{22}O_9$: C, 61.39; H, 5.12%.

The aqueous mother liquor from which the above ether had separated was evaporated somewhat and clarified with charcoal. On cooling, a small crop of colourless needles of meconine separated. Either alone or in admixture with an authentic specimen of meconine the product melted at 102° C.

3 : 4-Dimethoxy-6-methyl-phthalide (V)

The chloromethyl compound (III) (6 gm.) was heated overnight under reflux with zinc dust (5 gm.) in ethanol (100 cc.) containing hydrochloric acid (10 cc.). Additional hydrochloric acid was added until virtually all the zinc had dissolved. Water was added and the mixture extracted with ether. Removal of the solvent from the washed extract yielded a colourless oil that crystallized readily. It was recrystallized from hot water and obtained in colourless stout needles melting sharply at 127° C. The yield was virtually quantitative. Calc. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77%. Found: C, 63.54, 63.45; H, 5.95, 5.82%.

3-Ethoxy-4-methoxy-6-chloromethyl-phthalide (IV)

2-Ethoxy-3-methoxy-benzoic acid (II) (5 gm.) was boiled under reflux for 35 min. with 40% formaldehyde (12.5 cc.) and hydrochloric acid (20 cc.). The mixture, turbid at first, cleared completely, and then became turbid again. Water was added and the cooled mixture extracted with ether. The washed extract (bicarbonate) on evaporation yielded a residue that crystallized readily. When recrystallized from acetone, colourless fine needles melting at 130° C. were obtained. Yield, 3 gm. Calc. for $C_{12}H_{13}O_4Cl$: C, 56.14; H, 5.07; Cl, 13.84%. Found: C, 56.44, 56.57; H, 5.29, 5.03; Cl, 13.22, 13.49%.

3-Ethoxy-4-methoxy-6-hydroxymethyl-phthalide

The chloromethyl-compound (IV) when boiled with water dissolved slowly. Ether extraction of the cooled solution yielded a colourless halogen-free crystalline substance which when recrystallized from boiling water melted at 120° C. Calc. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88; OMe, 26.05%; mol. wt. 238. Found: C, 60.66, 60.36; H, 5.97, 5.70; OMe, 26.01%; mol. wt. 243, 236 (Rast).

3-Ethoxy-4-methoxy-6-cyanomethyl-phthalide

The chloromethyl-compound (IV) (7 gm.) was dissolved in a solution of sodium methylate (0.7 gm. of sodium in 50 cc. of absolute methanol) to which

had been added an excess of anhydrous hydrogen cyanide and the mixture heated on a steam bath for an hour. Water was added and the oil extracted with ether. The residue from the washed extract was distilled *in vacuo* (b.p. 145° (2 mm.)) and recrystallized from acetone–ether, yielding colourless prisms melting at 132° C. (3 gm.). Calc. for $C_{13}H_{13}O_4N$: C, 63.16; H, 5.26; N, 5.67%. Found: C, 63.21; H, 5.39; N, 5.63%.

3-Ethoxy-4-methoxy-6-carboxymethyl-phthalide

A solution of the above cyanomethyl-compound (2 gm.) in ethanol containing an excess of sodium hydroxide was heated under reflux for 24 hr. and then evaporated to dryness on the steam bath. The residue was dissolved in dilute hydrochloric acid and the solution extracted with ether. The dried residue from the ether extract was recrystallized from ether and obtained in fine colourless needles melting at 151° C. (1.5 gm.). Calc. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.26%. Found: C, 58.53, 58.73; H, 5.29, 5.20%.

3-Ethoxy-4-methoxy-6-methyl-phthalide (X)

The reduction of the chloromethyl-compound (IV) followed in detail the procedure given for the preparation of 3 : 4-dimethoxy-6-methyl-phthalide (V). The product was recrystallized from acetone and obtained in colourless plates melting at 119° C. Calc. for $C_{12}H_{14}O_4$: C, 64.87; H, 6.31%. Found: C, 64.74, 64.86; H, 6.61, 6.49%.

2-Hydroxy-3-methoxy-5-methyl-benzaldehyde (XV)

This aldehyde has been described as an oil (6) prepared from commercial creosol and chloroform in the presence of alkali. When prepared from pure creosol by the same procedure it was obtained as a pale yellow solid albeit in poor yield. The large quantity of creosol that was required was made by the procedure of Fletcher and Tarbell (2). The details are slightly different, and are as follows: a mixture of zinc amalgam (100 gm.), water (75 cc.), vanillin (50 gm.), toluene (100 cc.), and hydrochloric acid (150 cc.) was boiled under reflux for 24 hr., additional hydrochloric acid being added until a total of 275 cc. was used. The mixture was then distilled in a current of steam until the toluene and the phenol had passed over. The toluene layer was fractionated *in vacuo* and the creosol obtained in 60% yield (b.p. 108° (14 mm.)).

Better yields of the aldehydes were obtained by the procedure of Duff (1). A mixture of glycerol (150 gm.) and boric acid (35 gm.) was heated until the temperature reached 170° C. Hexamethylene-tetramine (25 gm.) was added, the temperature being maintained at 170° C. during the addition, and then allowed to fall to 160° C. when the phenol (25 gm.) was added in one portion and the temperature held at 150 to 155° C. for 15 min. The mixture was next cooled to 110° C., diluted with a solution of sulphuric acid (30 cc.) in water (100 cc.), and then distilled in a current of steam. The aldehyde, which distilled readily, crystallized in the condenser. It was separated by ether extraction. The yield was uniformly 11 to 12 gm. A portion recrystallized from hexane was obtained in pale yellow stout prisms melting sharply

at 77° C. Calc. for $C_9H_{10}O_3$: C, 65.06; H, 6.02%. Found: C, 64.90, 65.03; H, 5.86, 6.09%.

The *oxime* crystallized readily from boiling water and melted at 165° C. Calc. for $C_9H_{11}O_3N$: N, 7.74%. Found: N, 7.67, 7.80%.

2 : 3-Dimethoxy-5-methyl-benzaldehyde (XVI)

The above hydroxy-aldehyde was alternately treated with dimethyl sulphate and 40% aqueous sodium hydroxide until the yellow sparingly soluble sodium salt of the phenol had all reacted. A large excess of reagents was necessary but the yield of methylated aldehyde was good. The oil was removed by ether extraction and the residue from the washed extract, which crystallized readily, was recrystallized from warm hexane in which it is readily soluble, yielding colourless elongated plates melting at 40° C. Calc. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67; OMe, 34.44%. Found: C, 66.40, 66.23; H, 6.19, 6.17; OMe, 33.20, 33.35%.

The *oxime*, recrystallized from boiling water, was obtained in colourless needles melting at 99° C. Calc. for $C_{10}H_{13}O_3N$: N, 7.18%. Found: N, 7.23, 7.21%.

2 : 3-Dimethoxy-5-methyl-cinnamic Acid

A mixture of the aldehyde (XVI) (22 gm.), malonic acid (22 gm.), pyridine (50 gm.), and two drops of piperidine was heated on a steam bath until evolution of carbon dioxide ceased, and then heated just to gentle boiling. The somewhat cooled mixture was rendered just acid with dilute hydrochloric acid. The precipitated crystalline acid was filtered off, washed, and dried. Yield, 24 gm. A portion recrystallized from boiling dilute acetic acid was obtained in colourless plates melting at 188° C. Calc. for $C_{12}H_{14}O_4$: C, 64.87; H, 6.31%. Found: C, 64.86, 65.00; H, 6.34, 6.35%.

β-(2 : 3-Dimethoxy-5-methyl) phenyl-propionic Acid

The above cinnamic acid was reduced with 4% sodium amalgam in aqueous solution until a test portion no longer decolorized aqueous permanganate immediately. The recovered acid was recrystallized from benzene–hexane and thus obtained in colourless fine needles melting sharply at 63° C. Calc. for $C_{12}H_{16}O_4$: C, 64.30; H, 7.14%. Found: C, 64.44, 64.10; H, 6.91, 6.94%.

2 : 3-Dimethoxy-5-methyl-benzoic Acid (VIII)

The corresponding aldehyde (XVI) was suspended in warm water through which a stream of carbon dioxide was being passed and the stirred mixture gradually treated with solid potassium permanganate until the colour due to the latter was permanent. The acid was isolated from the filtered and acidified solution by ether extraction and recrystallized from hot water. It melted at 91° C. Three grams of purified acid was obtained from 5 gm. of the aldehyde.

3 : 4-Dimethoxy-6-methyl-phthalide (V)

A mixture of the acid (VIII) (2 gm.), 40% formaldehyde (5 cc.), and hydrochloric acid (8 cc.) was gently heated over a free flame for 35 min. The

homogeneous solution became turbid after several minutes of heating. On diluting with water and cooling, the separated oil readily crystallized. It was filtered off, washed, and recrystallized from hot water. The fine colourless needles, obtained in virtually quantitative yield, were completely free of halogen, and they melted sharply at 127° C. either alone, or in admixture with a specimen prepared by reduction from the chloromethyl-phthalide (III).

2-Ethoxy-3-methoxy-5-methyl-benzaldehyde (XVII)

The ethylation of the aldehyde (XV) was even more difficult than the methylation. Ultimately a good yield of an impure product was obtained. The aldehyde melted at about room temperature.

2-Ethoxy-3-methoxy-5-methyl-cinnamic Acid

This acid was obtained in excellent yield by the procedure detailed for the dimethoxy acid. It was recrystallized from dilute acetic and obtained in yellow stout needles melting at 168° C. Calc. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78%. Found: C, 66.30, 66.10; H, 6.90, 6.59%.

β-(2-Ethoxy-3-methoxy-5-methyl) phenyl-propionic Acid

Reduction of the above cinnamic acid proceeded smoothly and the *propionic* acid when recrystallized from benzene–hexane consisted of colourless fine needles melting at 100° C. Calc. for $C_{13}H_{18}O_4$: C, 65.54; H, 7.56%. Found: C, 65.34, 65.49; H, 7.61, 7.51%.

2-Ethoxy-3-methoxy-5-methyl-benzoic Acid (IX)

The *acid* was obtained in 80% yield by oxidizing the aldehyde (XVII) with aqueous potassium permanganate. When recrystallized from hot water it was obtained in colourless elongated plates melting at 89° C. Calc. for $C_{11}H_{14}O_4$: C, 62.87; H, 6.67%. Found: C, 63.08, 62.82; H, 6.49, 6.69%.

3-Ethoxy-4-methoxy-6-methyl-phthalide (X)

A quantitative yield of this phthalide was obtained when the above benzoic acid (IX) (1 gm.) was heated for 35 min. with 40% formaldehyde (2.5 cc.) and hydrochloric acid (4 cc.). The crude product was free of chlorine and when recrystallized from hot water (charcoal) it melted at 119° C. either alone or in admixture with a specimen obtained from the chloromethyl-phthalide (IV).

3-Hydroxy-4-methoxy-6-methyl-acetophenone (XIII)

A mixture of creosol (XI) (15 gm.) and acetic anhydride (10 gm.) containing a drop of sulphuric acid was heated to 100° C. for a short time, cooled, diluted with water, and extracted with ether. The ether extract was washed with aqueous sodium hydroxide and then with water. The residue remaining when the ether was evaporated was distilled *in vacuo*, yielding 17 gm. of colourless acetyl-creosol (XII) (b.p. 136° C. (12 mm.)). The latter was added to a cooled solution (10° C.) of aluminium chloride (27 gm.) in nitrobenzene (60 cc.). The mixture was then slowly heated to 80° C. and maintained at this temperature for an hour, during which time the addition compound

separated in crystalline condition. The cooled mixture was decomposed with ice and dilute hydrochloric acid and the nitrobenzene removed in a current of steam. The residual oil, which crystallized readily on cooling, was filtered off and washed. (The filtrate was extracted with ether. The extract was recrystallized from hot water and the more soluble fractions systematically reworked. There was ultimately obtained about 1 gm. of colourless plates of 3 : 4-dihydroxy-6-methyl-acetophenone which melted sharply at 169° C. Calc. for $C_9H_{10}O_3$: C, 65.06; H, 6.02%. Found: C, 65.17, 65.21; H, 6.04, 5.86%. Methylation of this dihydroxy compound yielded 3 : 4-dimethoxy-6-methyl-acetophenone, identical with the same compound described below). The yield was about 70%. It was conveniently recrystallized from hot water in which it is only sparingly soluble. It consisted of stout colourless prisms melting at 129° C. Calc. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67%. Found: C, 66.59, 66.65; H, 6.60, 6.60%.

3 : 4-Dimethoxy-6-methyl-acetophenone (XIV)

The methylation of the acetophenone (XIII) with dimethyl sulphate and aqueous sodium hydroxide proceeded with exceptional ease. The yield was quantitative and when recrystallized from 50% ethanol the ketone was obtained in colourless needles melting at 76° C. Calc. for $C_{11}H_{14}O_3$: OMe, 31.99%. Found: OMe, 31.83, 32.08%. The corresponding 3-ethoxy derivative melted at 63° C. Calc. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69%. Found: C, 69.35, H, 7.61%.

Isonitroso-3 : 4-dimethoxy-6-methyl-acetophenone

To a solution of sodium (2.3 gm.) in absolute ethanol (80 cc.) was added the above ketone (XIV) (17 gm.) and butyl nitrate (13 gm.). The homogeneous solution was allowed to remain in the ice chest for several days and the sodium salt which had then separated filtered off and washed with ether. It was decomposed with dilute acetic acid and the *isonitroso-ketone* recrystallized from dilute ethanol, thus yielding colourless plates melting at 122° C. Calc. for $C_{11}H_{13}O_4N$: N, 6.28%. Found: N, 6.23, 6.25%.

3 : 4-Dimethoxy-6-methyl-benzoic Acid (VI)

The isonitroso-ketone (above) was dissolved in aqueous sodium hydroxide and the solution heated until the yellow colour had largely faded. The addition of hydrochloric acid liberated hydrogen cyanide and precipitated 3 : 4-dimethoxy-6-methyl-benzoic acid, which, after recrystallization from hot water, melted sharply at 147° C. either alone or in admixture with an authentic specimen.

Addendum

The following compounds were prepared either as intermediates or to complete a series of derivatives of compounds obtained in various phases of this work.

2-Ethoxy-3-methoxy-cinnamic Acid

A mixture of 2-ethoxy-3-methoxy-benzaldehyde (10 gm.), malonic acid (10 gm.), pyridine (20 gm.), and a trace of piperidine yielded the cinnamic

acid (10 gm.). It was obtained from hot methanol in lustrous plates melting at 152° C. Calc. for $C_{12}H_{14}O_4$: C, 64.87; H, 6.36%. Found: C, 64.92, 64.87; H, 6.48, 6.51%.

Reduction with sodium amalgam yielded β-(2-ethoxy-3-methoxy) phenyl-propionic acid, which, when recrystallized from benzene–hexane, consisted of colourless needles melting at 64° C. Calc. for $C_{12}H_{16}O_4$: C, 64.28; H, 7.14%. Found: C, 64.04, 64.20; H, 7.15, 7.15%.

2-Methyl-3-ethoxy-4-methoxy-cinnamic Acid

This acid was obtained in almost quantitative yield from 2-methyl-3-ethoxy-4-methoxy-benzaldehyde (4). It was recrystallized from methanol, and it then consisted of lustrous plates melting at 186° C. Calc. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78%. Found: C, 65.92, 66.01; H, 6.88, 6.78%.

When the above acid was reduced with sodium amalgam it yielded β-(2-methyl-3-ethoxy-4-methoxy)-phenyl-propionic acid, which, when recrystallized from benzene, consisted of colourless fine needles melting at 121° C. Calc. for $C_{13}H_{18}O_4$: C, 65.49; H, 7.62%. Found: C, 65.51, 65.28; H, 7.72, 7.64%.

3-Ethoxy-2-methoxy-benzoic Acid

The authors gratefully acknowledge their indebtedness to the Monsanto Chemical Co., St. Louis, Missouri, for a gift of 3-ethoxy-2-hydroxy-benzaldehyde. From the aldehyde (210 gm.), dimethyl sulphate (225 gm.) and sodium hydroxide (80 gm. in 150 cc. of water) there was obtained 220 gm. of 3-ethoxy-2-methoxy-benzaldehyde boiling at 118° C. (1 mm.).

A portion of the aldehyde was oxidized with aqueous potassium permanganate. The 3-ethoxy-2-methoxy-benzoic acid was recrystallized from warm water, and was obtained in colourless needles melting at 64° C. Calc. for $C_{10}H_{12}O_4$: C, 61.19, H, 6.17%. Found: C, 61.09, 61.35; H, 6.31, 6.43%.

3-Ethoxy-2-methoxy-cinnamic Acid

This acid was obtained in excellent yield from the corresponding aldehyde. When recrystallized from methanol it was obtained in colourless fine needles melting at 184° C. Calc. for $C_{12}H_{14}O_4$: C, 64.87; H, 6.36%. Found: C, 64.92, 64.87%; H, 6.48, 6.51%.

Reduction of this acid yielded β-(3-ethoxy-2-methoxy)-phenyl-propionic acid, which, when recrystallized from benzene–hexane, melted at 66° C. Calc. for $C_{12}H_{16}O_4$: C, 64.28; H, 7.14%. Found: C, 64.04, 64.20; H, 7.15, 7.15%.

4 : 5-Dimethoxy-2-methyl-benzoic Acid (VI)

The aldehyde corresponding to this acid was prepared by Gattermann's procedure (3). From 57 gm. of 3 : 4-dimethoxy-toluene there was obtained 58 gm. of the pure aldehyde boiling at 153° C. (7 mm.). It was oxidized to the acid, which, when recrystallized from water, was obtained in colourless long needles melting at 147° C. (5).

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NOTE ON A THERMOSTATICALLY CONTROLLED MICROSCOPE HOT STAGE[1]

By I. E. Puddington[2]

Abstract

A microscope hot stage, capable of maintaining any desired temperature to within ±0.1° C. in the range from room temperature to 300° C., is described.

While numerous descriptions of hot stages for microscopes have been published (for example, (1), (2), (3)), most of these stages have been used for melting point or similar determinations where increase in temperature at a reproducible rate is required, and no provision has been made for maintaining the temperature constant at any particular level. Since it was desirable, in a particular piece of work, to make microscopic observations at constant, elevated temperatures, the stage described below was devised. This stage has proved useful in noting the behaviour of soap crystals in oil and starch granules in water, in the vicinity of the swelling temperature.

The apparatus consisted essentially of three brass plates approximately $2\frac{1}{2}$ in. square, and about 3/8, 1/8, and 1/16 in. in thickness. The bottom plate is shown in section in Fig. 1. Four 1/4 in. holes, *C*, served as wells for a four pronged mercury thermoregulator. Two similar holes, *A*, spaced as shown, contained the heating elements. These were made by wrapping clay rods with No. 35 nichrome wire and insulating with alundum cement. They had a total power of 60 watts. *B* is a thermometer well.

A section removed from the middle plate served as a slot into which a slide containing the sample could be placed. A hole somewhat larger than the objective lens to be used with the microscope was drilled through the plates to permit viewing the sample. After covering the plates with a thin layer of solder, they were assembled, while still hot, with a machine screw at each corner. This procedure gives better thermal conductivity between the layers.

The four pronged mercury thermoregulator with the heaters positioned between the prongs gave excellent temperature control. The use of about 0.7 mm. capillary cut down the dead space in the connecting tubing and provided sufficient sensitivity at the contact points. By using a suitable resistance in series with the heaters, temperatures could be maintained to within ±0.1° C. over a range from room temperature to 300° C. No difference in temperature could be detected between the sample chamber and the surrounding metal block after equilibrium was established.

During use, microscope cover glasses served as windows for the top and bottom orifices. A layer or two of asbestos paper provided sufficient heat

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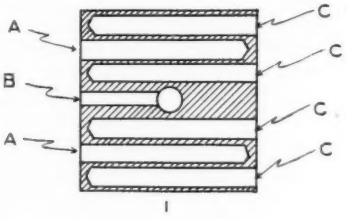
[2] *Chemist.*



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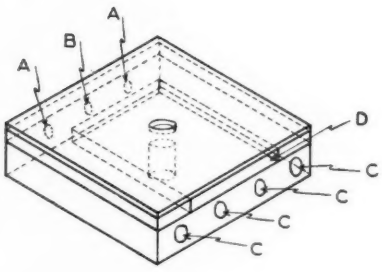

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FIG. 1. *Bottom plate in section.* FIG. 2. *Plates in assembled position. A, B, and C, wells for heaters, thermometer and thermoregulator; D, slot for microscope slide.*

insulation. When observations at high temperatures were being made, the microscope objective lens was protected by passing a stream of cool air, from a jet, directly under it.

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THE SEPARATION OF THE OXYGEN ISOTOPES BY THE DISTILLATION OF WATER[1]

By H. G. Thode[2], S. R. Smith[3], and F. O. Walkling[3]

Abstract

Three 25 ft. columns packed with "Haydite" aggregate, a cheap efficient packing material, have been operated in cascade for 120 days to concentrate the oxygen isotopes by the distillation of water. In this time 23 gm. of O^{18} in excess of normal were produced. This includes 150 ml. of water enriched 6.5-fold in O^{18} and 2.7-fold in O^{17}. The results indicate that these columns can be expanded to several feet in diameter for large scale production of O^{18} without much loss in efficiency. Cohen's theory for the operation of packed fractionating columns explains satisfactorily the effect of rate of flow on the equilibrium fractionation and gives a production rate in agreement with our data. The vapour pressure of H_2O^{17} has been calculated and found to be equal, within the limits of our experiments, to the algebraic or geometric mean of the vapour pressures of H_2O^{16} and H_2O^{18}.

Since Lewis and Cornish (5) first showed that a difference in vapour pressure existed between the two forms of water H_2O^{16} and H_2O^{18}, a number of attempts have been made to concentrate O^{18} by distillation. Stedman (8) used a crumpled stainless steel gauze column and effected small changes in the O^{18} concentrations. Later, Huffman and Urey (4) produced 0.85% O^{18} with a rotating funnel column. More recently, Randall and Webb (6) reported experiments with two packed columns operated singly, and similar concentrations of O^{18} were produced.

To separate the oxygen isotopes by distillation, very efficient columns of considerable length are required. It is also important for large-scale production to have inexpensive columns which are efficient in large diameters. In the past few years, a cheap efficient packing, "Haydite"* aggregate, has been developed in this laboratory. Tests by Thode and Walkling (10) indicate that this material is most efficient as a packing in fractionating columns, especially for water systems. Further, these tests showed that it was efficient in columns of large diameter. To concentrate large amounts of the heavy isotopes of oxygen for isotope exchange and tracer work, water has been distilled in a cascade system of columns packed with "Haydite" aggregate. Also several single column runs have been made to provide data for the application of Cohen's (1) theory for packed fractionating columns.

Apparatus

On the basis of preliminary runs, the apparatus (see Fig. 1) was designed to distil the water in a three stage cascade system, in which each unit produces a threefold change in the O^{18} isotope. Unit *A* is a 26 ft. glass column with

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Contribution from the Department of Chemistry, McMaster University, Hamilton, Ont.
[2] *Professor of Chemistry.*
[3] *Graduate student.*
* *"Haydite" aggregate packing manufactured by the Cooksville Company, Cooksville, Ont.*

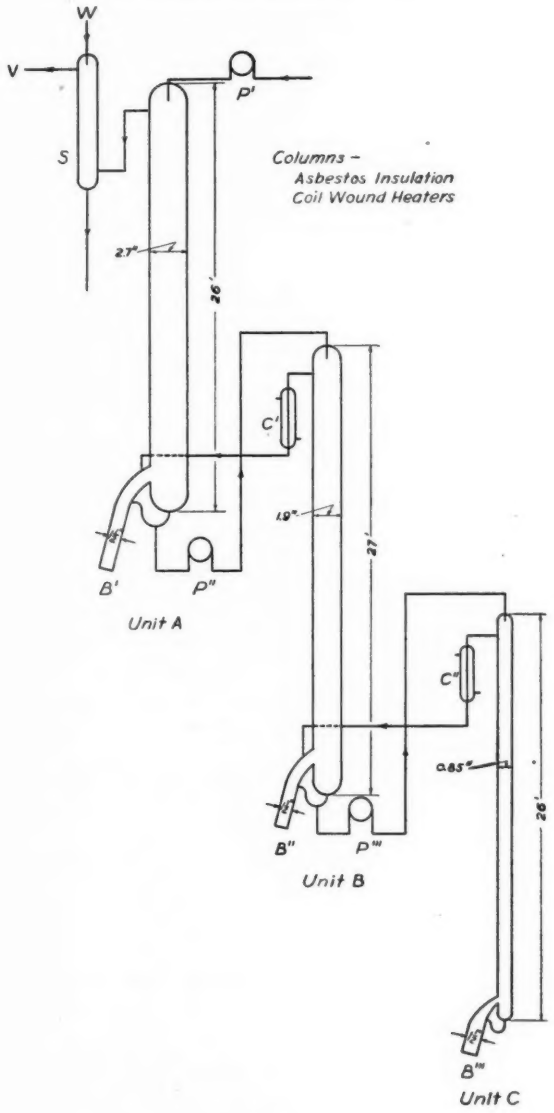

FIG. 1.

an inside diameter of 2.7 in. packed with 6 to 8 mesh "Haydite". Unit *B* is a 27 ft. glass column with an inside diameter of 1.9 in. packed with 6 to 8 mesh "Haydite". Unit *C* is a 26 ft. glass column with an inside diameter of 0.85 in. packed with 7 to 8 mesh "Haydite". The units are mounted in a

shaft 75 ft. high and are staggered to facilitate pumping liquid from the bottom of one unit to the top of the next.

Since the units operate above room temperature, each unit is insulated with several layers of 1/16 to 1/8 in. asbestos paper, wound with heaters, and provided with thermocouples for measuring temperatures. In this way adiabatic operation at the temperature of distillation is readily controlled.

The flash boilers that vaporize the water at the bottom of each unit are constructed of heavy copper tubing with an outside diameter of $1\frac{1}{2}$ in. These are insulated with asbestos paper and mica tape and are wound with heavy nichrome wire. The boilers of Units *A*, *B*, and *C* are 3 ft., 2 ft. and 1 ft. long respectively. This type of flash boiler is very satisfactory and has given no trouble during many months of operation.

Constant pressure is maintained at the top by means of a mercury regulator, a relay, and a vacuum pump.

Operation

The operation of the cascade system is similar to that described by Thode and Urey (9) for the separation of the nitrogen isotopes by chemical exchange. Pump P' pumps normal distilled water at the rate of 19 cc. per min. into the top of Unit *A*. Pump P'' pumps water enriched in O^{18} at the rate of 6 cc. per min. from the bottom of Unit *A* to the top of a smaller Unit *B*, and pump P''' pumps water further enriched at the rate of 2.1 cc. per min. from the bottom of Unit *B* to still smaller Unit *C*. The vapour from Unit *C* is condensed in C'' and passes as liquid into the boiler of Unit *B*; similarly the vapour from Unit *B* is condensed in C' and passes into the boiler of Unit *A*. Finally, the vapour from Unit *A* escapes through a cold water stripper *S*, and a vacuum leg to a drain. In operation, the pressure at the top of Unit *A* is maintained at 11 cm. of mercury. The back pressure through each unit is about 9 cm. of mercury. Since the units are operated in series, a pressure drop of 27 cm. would be expected across the three units. However, the vapour return line from Unit *B* to *A* was designed to give an aspirator action which reduced the pressure at the top of Unit *B*; hence the total pressure drop across the three units is less than the sum of the pressure drops across each unit. This aspirator action is desirable as it reduces the over-all pressure drop through a cascade system.

Any fluctuation in operation, such as the failure of a boiler or a feed pump, causes a change in the pressure drop across the units. An automatic signal system based on this principle notifies the operator of any failure.

The three feed pumps which are the only moving parts of the apparatus are an improved design of the gum rubber proportionating pump previously described (9). They are very satisfactory and will operate for several weeks at a time without attention.

Theory

Cohen (1) set up equations for isotopic exchange and fractional distillation in packed columns. His equations take the following form for the distillation of water where the heavy isotopes of oxygen concentrate in the liquid phase.

$$H\frac{\partial N}{\partial t} = L\frac{\partial N}{\partial z} - kcC\,[N(1-n) - \alpha\, n(1-N)] \tag{1}$$

$$h\frac{\partial n}{\partial t} = -l\frac{\partial n}{\partial z} + kcC\,[N(1-n) - \alpha\, n(1-N)] \tag{2}$$

where k is a constant, C is the concentration of oxygen per unit volume in the liquid, N is the mole fraction of heavy oxygen in the liquid, H is the number of moles of holdup per unit length of combined light and heavy oxygen in the liquid, L is the rate of flow of light and heavy oxygen in the liquid in moles per unit time, and the uncapitalized symbols designate the corresponding quantities for the gas phase. Z is the length of column measuring from the bottom (reflux end). For equilibrium between liquid and vapour the simple process separation factor is given by the equation

$$\alpha = \frac{N(1-n)}{n(1-N)} \tag{3}$$

and is also equal to the ratio of vapour pressures $P_{H_2O^{18}}/P_{H_2O^{18}}$. For the steady state with total reflux, $\frac{\partial N}{\partial t} = 0$ and $n = N$. Equations (1) and (2) are then easily solved to give

$$\ln\frac{R_0}{R_z} = (\alpha - 1)\frac{kcC\,Z}{L} \tag{4}$$

where R_0 and R_z are the isotopic ratios at the bottom and top of the column respectively. For the distillation of water with an infinite reservoir at the top R_z becomes the normal abundance ρ.

From Equation (4) it is seen that the enrichment factor is given by the approximate equation

$$\frac{R_0}{\rho} = \alpha^{\frac{kcC\,Z}{L}} \tag{4a}$$

which is the familiar equation for the plate columns and in which $\frac{kcC\,Z}{L}$ is the number of theoretical plates.

The factor kcC in Equations (1) and (2) is an exchange rate constant per unit length and will vary from column to column with the cross-sectional area. Reid and Urey (7) have, therefore, used the exchange rate constant per unit volume of $\frac{kcC}{A}$ as a measure of the fractionation efficiency of a column. This factor, which is to be maximized, can be calculated from the equilibrium enrichment factor $\frac{kcC\,Z}{L}$.

For a steady state with production P, $P = L - l$; $\frac{\partial N}{\partial t} = 0$, and introducing the boundary condition $n = N$ at $z = 0$, and solving Equation (1) we get

$$\left[\frac{(1 - p - \alpha)}{\frac{R_0}{\rho}(1 - p)(1 - \alpha)} + \frac{\alpha p}{(1 - p)(1 - \alpha)}\right]^{\theta(1-\alpha)} = \frac{1}{e^{2\sigma}} \tag{5}$$

where $p = \frac{P}{L}$, $\theta = \frac{1 - p}{1 - p - \alpha}$, and $e^{2\sigma}$ is the equilibrium fractionation factor. This equation is most useful in that for a given production concentration $\frac{R_0}{\rho}$, the production can be calculated provided the equilibrium fractionation $e^{2\sigma}$ is known.

Another aspect considered by Cohen is the time required for any given column to approach a steady state. Solving Equations (1) and (2) he obtains the skeleton equation

$$\frac{R_0}{\rho} = e^{2\sigma} - \frac{C_1 e^{-|p_1|t}}{\rho} - \frac{C_2 e^{-|p_2|t}}{\rho} \cdots \tag{6}$$

For systems where $\frac{l}{h} \gg \frac{L}{H}$ and $h + H \gg H(\alpha - 1)$ the term $- C_1 e^{-|p_1|t}$ is the largest and slowest to vanish and the time of coming to equilibrium is, therefore, determined by p_1. Putting in the value p_1 and neglecting other terms we get

$$\frac{R_0}{\rho} = e^{2\sigma} - K(\sigma) e^{-\frac{L}{HZ}(\alpha-1)2\sigma F(\sigma)t} \tag{7}$$

or

$$\ln\left[e^{2\sigma} - \frac{R_0}{\rho}\right] = \ln K(\sigma) - \frac{L}{HZ}(\alpha - 1)2\sigma F(\sigma)t \tag{8}$$

$F(\sigma)$ and $K(\sigma)$ are functions that can be determined if $e^{2\sigma}$ is known. Cohen has prepared a table giving the functions $F(\sigma)$ and $K(\sigma)$ for different values of $e^{2\sigma}$ (2).

Results

Samples of water, removed from the units at intervals of time, were equilibrated with carbon dioxide by the method of Cohn and Urey (3) and analysed with a mass spectrometer. With our instrument the O^{18} concentration can be obtained with a precision of better than 1%. The results of several single column runs are shown in Tables I to III.

The calculations made for these runs are summarized in Table IV. The $e^{2\sigma}$ or equilibrium fractionation given in Column 5 was obtained by plotting the left-hand side of Equation (8) as a function of time and choosing $e^{2\sigma}$ so that the calculated slope equals the measured slope. Another method was tried which does not involve a knowledge of liquid holdup H. $e^{2\sigma}$ is chosen so as to obtain the best straight line with a plot of $\ln\left[e^{2\sigma} - \frac{R_0}{\rho}\right]$ against time. Although the $e^{2\sigma}$ values obtained in this way check fairly well with

TABLE I

SINGLE COLUMN RUN I

Unit *A*. Diam. 2.7 in., length 26 ft. Temp. 58° C.

Sample	Time, days	Enrichment factor (O^{18})	Enrichment factor (O^{17})
1	9	1.63	1.18
2	12	1.61	
3	17	1.75	1.25
4	20	1.81	
5	26	1.91	1.38
6	29	1.98	1.39

TABLE II

SINGLE COLUMN RUN II

Unit *A*. Diam. 2.7 in., length 26 ft. Temp. 55° C.

Sample	Time, days	Enrichment factor (O^{18})
1	4	1.31
2	9	1.59
3	12	1.60
4	16	1.71
5	20	1.77
6	24	1.89

TABLE III

SINGLE COLUMN RUN III

Unit *A*. Diam. 2.7 in., length 26 ft. Temp. 100° C.

Sample	Time, days	Enrichment factor (O^{18})
1	3.75	1.20
2	4.75	1.22
3	5.75	1.24
4	6.75	1.265
5	7.75	1.29

the first method, the second method was far less sensitive and therefore unsatisfactory. The number of theoretical plates $\frac{kcC}{L}Z$ is calculated directly from Equation (4*a*). The operating efficiency of the column is given by the term $\frac{kcC}{A}$ listed in Column 7. The O^{18} separation factors used in the above calculations and listed in Column 3 were taken from the data of Wahl and Urey (11).

TABLE IV

SUMMARY OF SINGLE COLUMN RUNS

Unit *A*. Diam. 2.7 in., length 26 ft.

Run	Mean temp., °C.	α	Rate of flow, moles min.$^{-1}$	$e^{2\sigma*}$	$\frac{kcC\ Z^{**}}{A}$	$\frac{kcC}{A}$, moles cm.$^{-1}$ min.$^{-1}$	H.E.T.P., cm.
1(O^{18})	58	1.0063	1.39	2.1	118	3.6×10^{-2}	6.72
1(O^{17})	58	1.00315†	1.39	1.43	114	3.5×10^{-2}	6.95
2(O^{18})	55	1.0066	0.835	2.6	143	2.65×10^{-2}	5.54
3(O^{18})	100	1.003	1.055	1.6	149	3.46×10^{-2}	5.32

* *Steady state enrichment factor with no production.*
** *Number of theoretical plates.*
† *Value calculated below.*

As is usual, the long columns are less efficient than the short test columns used previously (10). However, 120 to 150 plates obtained with a 25 ft. 3 in. column is satisfactory when compared with results obtained with other packed columns, considering the long period of continued operation during which time the packing may become dry or accumulate a film of grease. Comparing Runs 1 and 2, it is seen that increasing the rate of flow L decreases the number of theoretical plates, but increases the operational efficiency factor $\frac{kcC}{A}$. It is, therefore, desirable to operate at the higher rates of flow and to use a longer column to obtain the higher equilibrium enrichment factor.

TABLE V

SUMMARY OF CASCADE OPERATION

Unit *A*. Diam. 2.7 in., length 26 ft.
Unit *B*. Diam. 1.9 in., length 27 ft.
Unit *C*. Diam. 0.85 in., length 26 ft.

Unit	H, cc.	O^{18} enrichment factor	Mean temp., °C.	α	$e^{2\sigma}$ estimated
A	7500	1.94	60.8	1.0061	2.3
B	4600	1.65	67.0	1.0056	2.4
C	750	2.00	75.0	1.0050	2.4
Over-all		6.45			14.4

The results of a 120 day run with the three units in cascade are summarized in Table V. When the concentration reached 1.35% O^{18}, production samples were removed each day for 20 days so as to maintain this concentration. It was found that at 5 ml. production per day the concentration increased slightly, whereas at 10 ml. per day the concentration decreased slightly.

This transport for Unit *C* is only about one-third the transport for Unit *A* since each unit was designed for production at threefold enrichment. Altogether 23 gm. of O^{18} in excess of the normal were produced. This includes 150 ml. of 1.35% O^{18} and all drainage samples ranging in concentration from 0.21 to 1.35%. This production of 23 gm. of O^{18} in excess of the normal in 120 days amounts to about 50% of that calculated for Unit *A*, assuming the transport to be constant and proportional to $(\alpha - 1)$. According to Cohen's theory, however, the transport is always less than $(\alpha - 1)$. Our efficiency of 50% for the distillation of water is in agreement with the 50% efficiency reported by Cohen for the chemical exchange process ($NaCN_{sol} - HCN_{gas}$) (1) used for the separation of the carbon isotopes.

Since the enrichment factor for Unit *C* remained fairly constant (2.14 to 2.05) during production of 7.5 ml. per day of 1.35% O^{18}, the equilibrium enrichment factor for Unit *C* can be calculated (Equation 5). This factor turns out to be 2.6, which is reasonable considering the factors 2.4 and 2.3 calculated for Units *A* and *B*. There is no explanation for the low enrichment factor obtained with Unit *B* in the cascade system, as Unit *B* gave a factor of 2.1 with production during a preliminary run.

The Vapour Pressure of H_2O^{17}

Since O^{18} concentrates in the distillation of water, it is to be expected that O^{17} will concentrate also, although to a lesser extent. Because of analytical difficulties previous workers have confined their attention to O^{18}. Carbon dioxide, which is usually used in the mass spectrometer analysis of O^{18}, is unsatisfactory for O^{17} because of the coincidence of $C^{13}O^{16}O^{16}$ and $C^{12}O^{16}O^{17}$. To avoid this difficulty, oxygen gas prepared by electrolysis was analysed directly. The normal concentration of O^{17} was found to be $0.039 \pm 0.001\%$ as compared to the accepted value of 0.040. In Table I are shown the O^{17} and O^{18} analyses for a single column run. To further check on the concentration of H_2O^{17}, samples of higher concentrations from the cascade system were also analysed. The results of these analyses are given in Table VI.

TABLE VI

COMPARATIVE DATA FOR O^{17} AND O^{18} ENRICHMENT

Samples removed from final unit of cascade system. Mean temp., 67° C.

Sample	O^{18} enrichment factor	O^{17} enrichment factor	$P_{H_2O^{16}}/P_{H_2O^{17}}$	$P_{H_2O^{16}}/P_{H_2O^{18}}$
1	3.14	1.81	1.0026	
2	4.18	2.10	1.0028	
3	5.62	2.43	1.0024	
4	5.8	2.57	1.0025	1.0056
			Av. 1.0026 ± 0.0002	

The two rare forms of water H_2O^{17} and H_2O^{18} concentrate simultaneously in the distillation of water. For this reason, all factors that determine the concentration of each, such as column characteristics, rates of flow, etc., will cancel, and only the initial concentrations and ratios of vapour pressures $P_{H_2O^{16}}/P_{H_2O^{17}}$, $P_{H_2O^{16}}/P_{H_2O^{18}}$ will differ. Since the initial concentrations are known and the vapour pressure of H_2O^{18} has been determined (11), the ratio $P_{H_2O^{16}}/P_{H_2O^{17}}$ and the vapour pressure of H_2O^{17} can be calculated.

This calculation can be made with the data of Run I, Table I, using Equation (8) above. The slope of the curve obtained by plotting $\ln\left[e^{2\sigma} - \frac{R_0}{\rho}\right]$ against time is equal to $-\frac{L}{HZ}(\alpha-1)2F(\sigma)$. By comparing the measured slope for the two isotopes relative values of $(\alpha - 1)$ can be calculated. The $e^{2\sigma}$ values used were taken from Table IV above. The corresponding $F(\sigma)$ can be read off a curve given by Cohen (2). By this method, α or the ratio $P_{H_2O^{16}}/P_{H_2O^{17}}$ is found to be 1.0033 ± 0.0002 at 58° C. as compared to 1.0063 for the ratio $P_{H_2O^{16}}/P_{H_2O^{18}}$.

The formula of Huffman and Urey, although approximate, is more suitable for the calculation of $P_{H_2O^{16}}/P_{H_2O^{17}}$ from the analysis of individual samples removed from Unit *C* as it does not involve the estimation of the equilibrium enrichment of the three units. The formula is as follows

$$(1 - N) \log \frac{1 - N}{1 - N_0} + N \log \frac{N}{N_0} = \frac{LN(\alpha - 1)k \log \alpha}{H} t, \qquad (9)$$

where N and N_0 are the mole fractions of the heavy isotope at the top and bottom of the column respectively at time t, and k is the number of theoretical plates. This formula was derived assuming the transport of the heavy constituent to be constant and equal to $LN(\alpha - 1)$. For the purpose of comparing the simultaneous concentration of O^{17} and O^{18}, this assumption seems justified, as the transports of the two isotopes will probably decrease in about the same proportion as the columns approach a steady state Since the two isotopes concentrate simultaneously, the time factor will be the same for the two isotopes, and the ratio $(\alpha - 1) \log \alpha$ for the two isotopes can be calculated. The ratios for $P_{H_2O^{16}}/P_{H_2O^{17}}$ thus obtained, are given in Column 4, Table VI.

These calculations indicate that the vapour pressure of H_2O^{17} is equal to the algebraic or geometric mean of the vapour pressures of H_2O^{16} and H_2O^{18}.

Discussion

"Haydite" packed columns used for the concentration of the oxygen isotopes by the distillation of water are efficient. Further, there is little difference in fractionation efficiency in columns from 1 to 3 in. in diameter. This fact suggests that the columns can be expanded to several feet in diameter for large-scale production without much loss in efficiency. In any system involving more than three columns it would be necessary to reduce the pressure at the top of each unit and thus lower the over-all back pressure so as to main-

tain the higher separation factors obtained at lower temperatures. The liquid holdup in this type of column is high compared with that of other columns, even taking into account the high efficiency. It has been found in this laboratory that the efficiency of the packing varies with the sample of material used. For example, "Haydite" packing prepared from material expanded at higher temperatures is more efficient especially when the particle is sharp and angular. Unfortunately, the above experiments were carried out with standard material. Further experiments are planned in co-operation with the Cooksville Company, Cooksville, Ont., in order to improve the efficiency and holdup characteristics of the packing.

An interesting feature of the packing used in our experiments is its drainage characteristics. When the feed liquid flow is stopped only about 15% of the liquid holdup drains from the columns. The remainder is held on the surface of the packing and it only drains slowly over a long period of time. In isotope separation work where the columns must operate over a long period of time, this is a desirable feature as the columns can be shut down for repairs without the complete mixing of all the column material.

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